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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,158	03/15/2001	Carol O. Cowing	LANCELL.002CP1	5364

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EXAMINER

CANELLA, KAREN A

ART UNIT PAPER NUMBER

1642

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/809,158

Applicant(s)

COWING, CAROL O.

Examiner

Karen A Canella

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1, 4-11, 13-19, 21-24, 27-31, 37, 42, 51-56, 58, 59 is/are pending in the application.
- 4a) Of the above claim(s) 4, 5, 7, 9, 10, 37, 42 and 59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-56 and 58 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date Dec 15, 2003.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

1. The text of sections of Title 35, US Code not found in this action can be found in a previous Office action.
2. Claims 1, 6, 8, 11, 24, 52 and 55 have been amended. Claims 58 and 59 have been added. Claims 2, 3, 12, 25, 26, 32-36, 38-41, 43-50, 54 and 57 have been canceled. Claims 4, 5, 7, 9, 10, 37 and 42 are withdrawn. Newly added claim 59, drawn to non-elected subject matter, is also withdrawn from consideration.
3. Claims 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 30 embodies the method of claim 1 wherein the amount of topical treatment is further characterized as being sufficient to increase the local release of an endogenous inducer of dendritic cell migration and maturation. Claim 31 embodies the method of claim 1 wherein the amount of topical treatment is further characterized as being sufficient to alter the plasma membrane expression of function of an adhesion molecule. The instant claims are reliant upon the identity of the endogenous inducer of dendritic cell migration and maturation and the plasma membrane expression of an adhesion molecule. The specification does not describe the structure of either of the endogenous inducer of dendritic cell migration and maturation, nor the expression of the adhesion molecule. Although drawn to DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* At

Art Unit: 1642

1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *Id.* At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.* thus the specification lacks an adequate written description for the endogenous inducer of dendritic cell migration and maturation and the adhesion molecule which is expressed on the plasma membrane. Because the specification lacks adequate written description of these products, it also lacks adequate written description for method claims reliant upon the identity of said products.

4. Claims 1, 6, 8, 11, 13, 14, 16, 28, 29, 30, 31, 55, and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30).

Dearman et al disclose a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al disclose that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-associated antigen. Dearman et al disclose that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al disclose that the results imply that exposure of FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Thus, Dearman et al

disclose the specific limitation of increasing the number of antigen bearing dendritic cells in a draining lymphoid organ. (page 29, first column, line 2 to second column, line 7).

5. Claims 1, 6, 8, 11, 13, 14, 16, 17, 21, 22, 27, 28, 29, 30, 31, 51, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Mitragotri et al (WO 97/04832) and Paul et al (Vaccine Research, 1995, Vol. 4, pp. 145-164, cited in a previous action).

The specific embodiments of claims 1, 6, 8, 11, 13, 14, 16, 28, 29, 30, 31, 55, and 56 are set forth above. Claim 17 is drawn to a method for vaccinating a mammal against an antigen comprising introducing into the mammal an effective dose of the antigen or an epitope thereof and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introducing the antigen and administering the treatment are performed independently in any order and wherein the topical treatment comprises application of ultrasound energy.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-associated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was an endogenous protein, or a method of topical immunization where the antigen was injected into the epidermis,

Art Unit: 1642

Paul et al disclose a method for vaccinating a mammal against an antigen comprising the topical administration of an antigen encapsulated in transfersomes. Paul et al disclose that the encapsulated protein traverses the stratum corneum by means of the ultradeformable submicroscopic transfersome vesicles (page 147, fourth full paragraph). Paul et al do not teach a method of immunization comprising a lipophilic molecule, or a method of increasing the number of antigen-bearing dendritic cells in a draining lymph node

Mitragotri et al teach that the passive skin permeability to high molecular weight proteins is essentially zero (page 29, line 35 to page 30, line 2). Mitragotri et al teach that ultrasound application induces significant transdermal permeation of large proteins such as insulin, gamma interferon and erythropoietin (page 21, lines 3-5). Mitragotri et al teach that high molecular weight proteins can be encapsulated in liposomes which are coated with lipophilic molecules in order to enhance penetration (page 23, lines 3-6 and page 23, line 21 to page 4, line 5).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer an endogenous protein antigen by means of intraepidermal or intradermal injection, ultrasound or ultrasound of encapsulated protein molecules, wherein the capsule is coated with lipophilic molecules, and wherein dibutyl phthalate was applied to the skin either before or after said ultrasound treatment. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the independent action of dibutyl phthalate on the acquisition of antigen by dendritic cells within draining lymph nodes wherein said antigen is delivered to the lymph nodes via Langerhans cells and the teachings of Mitragotri et al on the lack of penetration of large proteins into the stratum corneum without use of ultrasound or ultrasound in combination with encapsulated proteins. One of skill in the art would conclude that direct intraepidermal or intradermal injection of the protein antigen would be an alternative for the ultrasound permeation because it would place the protein antigen in proximity to Langerhans cells and thus would result in the transport of the antigen to the draining lymph nodes.

6. Claims 1, 18 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of King et al (Vaccine, 1987, Vol. 5, pp. 234-238, cited in a previous action).

Claim 24 is drawn to a method for vaccinating a mammal against an antigen comprising administering to the mammal an effective dose of an antigen or epitope thereof and a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells, wherein the antigen and the topical treatment are performed independently in any order wherein said topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and inducing dendritic cells to migrate to the draining lymph nodes and wherein the antigen or epitope thereof is introduced into the mammal by a transfer of cells containing the antigen or epitope thereof. Claim 18 embodies the method of claim 1 wherein the antigen or epitope thereof is introduced into the mammal by a virus, bacterium, fungus or parasite.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-associated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was introduced into the mammal by a transfer of cells containing the antigen or epitope thereof.

King et al disclose a method for vaccinating a mammal against an antigen comprising delivering to the nasal passages a topically applied live vaccine, thus fulfilling the specific embodiment of claim 18.

It would have been prima facie obvious at the time the invention was made to administer topical dibutyl phthalate either before or after the administration of the cellular vaccine of King et al. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the

increase in antigen-bearing dendritic cells in the draining lymph nodes observed after topical administration of dibutyl phthalate.

7. Claims 1, 18, 19, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Salyers et al (Bacterial Pathogenesis (text), 1994, pp. 8-14 and 144-145)

Claim 19 is drawn to a method for vaccinating a mammal against an antigen comprising introducing into the mammal an effective dose of the antigen or an epitope thereof and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introduction of the antigen is carried out by ingestion. Claim 23 embodies the method of claim 1 wherein the antigen or epitope thereof is introduced into the mammal via delivery to the gastrointestinal tract.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, , lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-associated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was introduced into the gastrointestinal tract by ingestion.

Salyers et al teach the colonization of the mucosal epithelium by natural pathogens (pages 144-145). Salyers et al teach that mucosal membranes of the intestinal tract have specialized mucosal associated lymphoid tissues for defense against ingested bacteria and other antigens (page 9, first column, first full paragraph). It would be prima facie obvious to one of skill

in the art that an antigen can be introduced into a mammal by ingestion, and that one could increase the number of antigen bearing dendritic cells within a draining lymph node by topical administration of dibutyl phthalate. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the induction of greater numbers of antigen-bearing dendritic cells within draining lymph nodes.

8. Claims 1, 6, 8, 11, 13-16, 27, 28-31, 52, 53, 55, 56 and 58 are rejected under 103(a) Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Glenn et al (US 5,980,898, cited in a previous action).

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-associated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was

Glenn et al disclose a method for vaccinating a mammal comprising the topical administration of an antigen such as a tumor antigen (column 3, lines 64-67 and column 15, lines 52-67) in a composition comprising an activator of Langerhans cells, wherein said activators include trinitrochlorobenzene, dinitrofluorobenzene, pentadecylcatechol and lipid A (column 11, lines 31-40), thus fulfilling the specific embodiments of a lipophilic molecule having a molecular weight less than or equal to 500 Daltons and an internal administration to the skin as an organ, thus fulfilling the specific embodiment of claim 56, drawn to delivery into an organ. Glenn et

Art Unit: 1642

al do not specifically teach embodiments of claim 58 drawn to increasing the number of antigen-bearing dendritic cells in a draining lymphoid organ it would be inherent in the method of Glenn et al that said dendritic cells would be increased.

9. The rejection of the claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55, 56 and 58 under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of US patent 6,210,672 is maintained for reasons of record. Acknowledgment is made of applicants intention of filing a terminal disclaimer at the time allowable subject matter is indicated.

10. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants arguemtns and amendments.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

Primary Examiner, Art Unit 1642

03/08/04


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER